REMARKS

Claim 7, 8, 10, 12, 14-18, 20 and 22-31 are currently pending. It is asserted that 8, 12, 14, 22 and 23 have been withdrawn. Thus, these claims are still pending. As will be discussed in further detail below, claim 7 has been amended to more distinctly claim that which Applicant regards as his invention. New claim 32 has been added to recite a specific embodiment.

1. **Claim Objections**

Claim 7, with dependent claims 10, 15-18, 20, 26, 27, 28, 30, 31, are objected to as reciting the non-elected subject matter of 5' and 3' non-coding regions and introns. Appropriate correction is required. Claim 7 has been amended accordingly to recite that it the region additionally is selected from the group consisting of "a contiguous exon-intron region" and "contiguous intron-exon region", both of which encompass the elected species, a splice junction.

2. **The Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 7, 10, 15-18, 20, 26-28, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is asserted that claim 7, with dependent claims 10, 15-18, 20, 26-28, 30 and 31, is unclear as reciting on lines 8-9 "or an isolated nucleic acid molecule of 20-51039 nucleotides consisting of SEQ ID N0:4". SEQ ID N0:4 is 51039 nucleotides and cannot consist of 20 nucleotides.

In response, claim 7 has been amended to recite "or an isolated nucleic acid molecule 20-51039 nucleotides in length consisting of SEQ ID NO:4". In view of the amendment of claim 7, the rejection has been overcome. Therefore, Applicant respectfully requests that the rejection be withdrawn.

6. **The Rejections Under 35 U.S.C. §103(a)**

Claims 7, 10, 15-20 and 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny et al, in view of Vogelstein et al. The Office Action states:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use said cDNA to identify the genomic DNA that encodes the human MDM2 homolog of SEQ ID NO: 2 on chromosome 12q12-14. The motivation is provided by Vogelstein et al. who teach that it binds to oncogene p53 and is diagnostic of tumorogenesis. The state of the art provides various techniques for obtaining genomic DNA using cDNA probes that are usually labeled. The comparison of genomic and cDNA would result in the identification of non-coding regions. One of ordinary skill in the art would have been motivated to use said non-coding regions or fragments thereof of at least 20 nucleotides for detecting variants of chromosome 12q12-14 from genomic nucleotide samples from an individual, for example. As a matter of convenience a non-coding region such as a splice junction or fragments thereof can be present in a kit or on a solid support. Further, said support can be a microarray to a customary use of nucleic acid molecules in the art.

It is further stated in the Office Action that

> With regard to the 103(a) rejection, Applicants argue that "As previously argued, there would not be any motivation to combine Muzny et al with Vogelstein et al. Muzny et al knew that clone AC025423 (from 1V11-61102) was from chromosome 12 but there is no evidence in the NCBI report of a sub-assignment to the p- or q-arm. Chromosome 12 is about 130 million base pairs long and is believed to contain several hundred genes ..... Further, there is no evidence that Muzny et al. knew whether the clone did or did not contain one or more genes and particularly whether it contained the gene encoded by SEQ ID NO:4. Vogelstein et al. placed the human MDM2 homologue gene at 12q12-14. Actually, this finding is incorrect. After the publication of Vogelstein the gene was found to be located at 12q12-14, whereas the gene is actually several millions of base pairs away at 12q15.....
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> There was actually a previous disclosure stating that the MDM2 was located between 12q14.3-15 (see, for example, Andersen et al., 1996, Mammalian Genome 7:780-783 and Bureau, 1995, Genomics 28: 109-1 12, submitted herewith as an IDS). However, given the conflicting locations published, one of ordinary skill in the art would not have known which location was actually correct. Clearly combining the disclosures of Muzny et al. with Vogelstein et al. would not have produced the claimed sequences, especially given Vogelstein's mistaken assignment of MDM2 to 12q12-14" .....This is not persuasive because it is well known in the art that the localization on the

chromosome is often imprecise. However, one of ordinary skill in the art would have been motivated to search the cDNA sequence against the entire genomic DNA in order to find the identical regions.

Applicants further argue that "Finally, Applicant would like to address the assertion made on page 15 of the instant Office Action. In re Deuel was merely being cited for the teaching that "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." However, although as noted in the Office Action, no nucleic acid sequence was known in Deuel, analogies may be drawn. In Deuel, the amino acid sequence was known yet the nucleic acid sequence was not known. It was held that given the large number of possible sequences, one of ordinary skill in the art would not be able to predict the correct sequence. It was actually stated in Deuel that "No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared". In the instant application, there is a chromosomal DNA sequence. However, there is nothing in Vogelstein which would lead one of ordinary skill in the art to Muzny et al. to indicate that the claimed sequences could actually be found in that clone. Furthermore, Applicant again wishes to emphasize that a sequence in and of itself does not predict whether or not a gene is present and certainly says nothing of which specific gene is present, if present at all" (pages' 15-16). This is not persuasive because the sequences, including comprising exon-intron junctions are contained within a known genomic DNA. There is no large number of sequences from which to choose but only a single one. This what is different between the current issue and the one considered in Deuel.

Applicant respectfully traverses the rejection. First, given that Muzny only discloses the sequence of the clone AC025423 but does not suggest that SEQ ID NO:4 or any other gene could be located on this clone and given that Vogelstein only provides a rough location for the MDM2 gene and the cDNA sequence which only constitutes a very small portion of the genomic sequence, one of ordinary skill in the art as of the priority date would not have had a reasonable expectation of success of obtaining the genomic sequence and subsequently the introns. At best, as pointed out in the Office Action, there may have been a motivation to search the cDNA sequence against the entire genomic DNA in order to find the identical regions but not necessarily a reasonable expectation of success. However, that is not

sufficient. The MDM2 cDNA sequence only constitutes just 1.6% of the sequence present on AC025423. One of ordinary skill in the art would not have known where in the remaining 98.4% of the sequence the remaining genomic sequence encoding MDM2 was located. Applicant notes that Vogelstein et al. had sufficient motivation to seek the MDM2 gene and define its organization but did not do so. At best, it would just be an "obvious to try" situation. It is well known that the "obvious to try" standard is clearly erroneous. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988).

An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). Here, only a general location is provided. It is further noted in the Office Action that the sequences, including exon-intron junctions are contained within a known genomic DNA. However, as stated above, SEQ ID NO:4 was not isolated. Furthermore, Vogelstein only disclosed the MDM2 cDNA sequence. No indication was given as to where and how many splice junctions may be located within this sequence or if alternative splicing was occurring. Even if one of ordinary skill in the art used probes containing splice junction consensus sequences to identify such sequences present on the Muzny sequence, at best one of ordinary skill in the art would not know whether it belonged to the MDM2 gene or some other gene present on this sequence. It would not have been possible to ascertain, isolate and determine the function of the noncoding region of the MDM2 gene until the genomic gene sequence itself had been defined.

As noted in the response to the previous Office Action, it turns out that the Vogelstein disclosure was actually incorrect. The Examiner asserts that it is well known that localization on the chromosome is often imprecise. However, would one of ordinary skill in the art upon discovering the error have continued to search AC025423 to isolate SEQ ID NO:4 and ultimately the introns? Obtaining any answer to this question would involve the use of hindsight. Such hindsight discounting is not permissible. *Ruiz v. A.B. Chance*, 357 F.3rd 1270 (Fed. Cir. 2004).

Finally, Applicant wishes to respond to the assertion made in the Office Action that in contrast to *Deuel* there is no large number of sequences from which to choose but only a

single one. First, there are a large number of sequences to choose from, the sequences contained within AC025423; the permutations and combinations are indeed significant given that the cDNA only constitutes such a minute portion (1.6%) of the AC025423 sequence. Second Deuel, does cite another case of particular relevance, *In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1993). In Bell, the court held that a reference disclosing a general method for isolating genes in combination with prior art disclosing amino acid sequences for insulin-like growth factors (I and II) (IGF) does not render obvious claims for nucleic acid molecules encoding IGF I and II. The court in *Bell* held that "given the nearly infinite number of possibilities suggested by the prior art and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious". Analogously, the prior art discloses the known MDM2 cDNA and there are large numbers of possibilities as to which sequences may be the genomic sequence but no suggestion as to which possibility is indeed the genomic sequence. Furthermore, even with the isolation of the genomic sequence, no direction ahs been given as to the number and location of noncoding regions. There are also a number of unanswered questions with respect to the structure of the MDM2 gene: (1) the size of the gene itself; (2) the number of introns; (3) the size of the introns and (4) the size of the 5' and 3' noncoding regions. As in *Bell*, no direction was provided.

Applicant also notes that *Bell* as in *Deuel* states "The PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not the method by which they are made". Here the Examiner appears to stress that techniques are known for obtaining genomic DNA using cDNA probes that are usually labeled. Therefore, the genomic sequence, SEQ ID NO:4 and the noncoding region would be obvious. This is erroneous according to the standard set by *Bell* and *Deuel*.

In view of the above arguments, Applicants assert that the rejections under 35 USC 103 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

7. Conclusion

In view of the foregoing, Applicants assert that the claims are now in condition for

allowance. Early action to that end is respectfully requested. The Examiner is invited to contact the undersigned at (914) 712-0093 if she has any questions.

Respectfully submitted,

Date: 6/8/06

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